Texas Medicaid/CHIP Vendor Drug Program
Drug Utilization Criteria For Outpatient Use Guidelines
Oral Histamine H2-Receptor Antagonists

About
Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

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1. Dosage [*]
Histamine H_2-receptor antagonists (H2RAs) are FDA-approved for use in gastric ulcer, duodenal ulcer, gastroesophageal reflux disease (GERD), esophagitis, hypersecretory conditions, and nonulcer indigestion/heartburn.

Adults
The maximum adult H2RA daily doses when prescribed FDA-approved conditions are summarized in Table 1. Dosage regimens exceeding these maximum recommended values will be reviewed.

Table 1: Adult Maximum Recommended Doses for H2RAs	
Drug Name	**Maximum Recommended Dose**
cimetidine (generics)	*acute therapy:* • GERD: 1600 mg/day • duodenal ulcer, gastric ulcer: 1200 mg/day • hypersecretory conditions: 2400 mg/day • heartburn: 400 mg/day • ***Helicobacter pylori* eradication*: 1200 mg/day in divided doses** *maintenance dose:* • duodenal ulcer: 400 mg/day • hypersecretory conditions: 2400mg/day
famotidine (Pepcid®, generics)	*acute therapy:* • duodenal ulcer, gastric ulcer, GERD: 40 mg/day • esophagitis: 80 mg/day • ***Helicobacter pylori* eradication*: 40 mg/day in single or divided doses** • hypersecretory conditions: 640 mg/day • heartburn: 40 mg/day *maintenance dose:* • duodenal ulcer: 20 mg/day • hypersecretory conditions: 640 mg/day
nizatidine **(generics)**	*acute therapy:* • duodenal ulcer, gastric ulcer, GERD **(including GERD-associated heartburn)**: 300 mg/day **in single or divided doses** *maintenance dose:* • duodenal ulcer: 150 mg/day **at bedtime**
ranitidine (Zantac®, generics)	*acute therapy:* • duodenal ulcer, gastric ulcer, GERD, **heartburn**: 300 mg/day in single or divided doses • **hypersecretory conditions: 6 g/day in divided doses** • erosive esophagitis: 600 mg/day *maintenance dose:* • duodenal ulcer, gastric ulcer: 150 mg/day at bedtime • erosive esophagitis, GERD: 300 mg/day **in two divided doses** • hypersecretory conditions: 6 g/day in divided doses

in combination with bismuth subsalicylate, metronidazole, and tetracycline; quadruple regimens containing H2RAs not as effective as proton pump inhibitor regimens in H. pylori eradication

Current American College of Gastroenterology guidelines state that **quadruple therapy regimens, while FDA-approved, are associated with lower compliance and efficacy rates compared to other available proton pump inhibitor (PPI) regimens. H2RAs (e.g., famotidine 20 mg twice daily) are used in those patients requiring bismuth quadruple therapy for *Helicobacter pylori* management who are penicillin allergic or do not tolerate PPIs.**

Pediatrics
Maximum recommended pediatric H2RA daily doses for acute and maintenance therapy are summarized in Table 2. Dosages exceeding these recommendations will be reviewed.

Table 2: Pediatric Maximum Recommended Doses for H2RAs	
Drug Name	**Maximum Recommended Dose**
cimetidine	acute therapy: *≥ 12 years of age:* • heartburn: 400 mg/day **≤ 15 years of age:** • **GERD/esophagitis, duodenal ulcer, gastric ulcer: 20-40 mg/kg/day in divided doses** *≥ 16 years of age:* • duodenal ulcer: 1200 mg/day • gastric ulcer: 1200 mg/day • GERD: 1600 mg/day maintenance dose: *≥ 16 years of age:* • duodenal ulcer: 400 mg at bedtime
famotidine	acute therapy: *< 3 months of age:* • GERD: 0.5 mg/kg/day *3 months of age to < 1 year of age:* • GERD: 1 mg/kg/day (in two divided doses) *1 year of age to 16 years of age:* • duodenal ulcer, gastric ulcer: 0.5 mg/kg/day up to 40 mg/day at bedtime **in single or divided doses** • GERD: 2 mg/kg/day up to 80 mg/day **in two divided doses** *≥ 12 years of age:* • heartburn: 40 mg/day
nizatidine	acute therapy: *≥ 12 years of age:* • GERD **(including GERD-associated heartburn)**, esophagitis: 300 mg/day
ranitidine	acute therapy: *≥ 1 month of age to 16 years of age:* • duodenal ulcer, gastric ulcer: 8 mg/kg/day up to 300 mg/day • erosive esophagitis, GERD: 10 mg/kg/day in divided doses *≥ 12 years of age:* • heartburn: **300 mg/day** ***> 16 years of age:*** • **erosive esophagitis: 600 mg/day in four divided doses** • **duodenal ulcer, gastric ulcer, GERD: 300 mg/day in two divided doses** • **hypersecretory conditions: 6 g/day in divided doses** maintenance dose: *≥ 1 month of age to 16 years of age:* • duodenal ulcer, gastric ulcer: 4 mg/kg/day, up to 150 mg/day at bedtime ***> 16 years of age:*** • **duodenal ulcer, gastric ulcer: 150 mg/day at bedtime** • **erosive esophagitis: 300 mg/day in two divided doses** • **hypersecretory conditions: 6 g/day**

Dosage in Renal Impairment

H2RAs are primarily renally excreted. Dosage modifications for H2RA use in renal impairment are summarized in Table 3.

Table 3: H2RA Dosage Modifications in Renal Impairment	
Drug Name	**Dosage Adjustments in Renal Impairment**
cimetidine	• moderate impairment (CrCl 10-50 ml/min): 50% of total daily dose • severe impairment (CrCl < 10 ml/min): 300 mg orally every 12 hours; may increase to every 8 hours cautiously based on patient response
famotidine	moderate to severe impairment (CrCl < 50 ml/min): reduce total daily dose by 50%; alternately, dosing interval may be lengthened to 36-48 hours based on patient response and degree of renal impairment
nizatidine	*active treatment:* • CrCl 20-50 ml/min: 150 mg/day orally • CrCl < 20 ml/min: 150 mg orally every other day *maintenance therapy:* • CrCl 20-50 ml/min: 150 mg every other day orally • CrCl < 20 ml/min: 150 mg every 3 days orally
ranitidine	CrCl < 50 ml/min: 150 mg/day orally; may increase to every 12 hours cautiously based on patient response

CrCl = creatinine clearance

2. Duration of Therapy

Adult and Pediatric Patients

Clinical trials document a maximum treatment duration of 56 days (eight weeks) for anti-ulcer therapy in treating acute duodenal and gastric ulcers. In pediatric patients, a maximum GERD acute treatment duration of 8 weeks is recommended. H2RA treatment regimens at acute dosage levels lasting longer than four months will be reviewed.

When used as a component of bismuth quadruple therapy for H. pylori eradication in adults, **cimetidine or famotidine therapy should be continued in combination with bismuth subsalicylate, metronidazole, and tetracycline for 10 to 14 days. Cimetidine or famotidine therapy should be continued for 2 to 4 weeks after antibiotic discontinuation to guarantee appropriate healing of the acute ulcer.**

When used for nonulcer indigestion/heartburn, H2RA treatment duration should not exceed 14 days at the maximum dose, unless directed by a physician.

Maintenance therapy, at recommended daily maintenance doses (Tables 1 and 2), may be continued indefinitely based on patient need.

3. Duplicative Therapy [*]

The combination of two or more H2RAs is not supported by the current literature. Therefore, concurrent use of this combination will be reviewed as there is no clinical evidence to suggest that adjunctive administration improves outcome.

4. Drug-Drug Interactions [*]

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Table 4 summarizes major drug-drug interactions considered clinically relevant for H2RAs. Only those drug-drug interactions identified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed:

Table 4: Major H2RA Drug-Drug Interactions

Target Drug	Interacting Drug	Interaction	Recommendations	Clinical Significance*+
cimetidine	clopidogrel (Plavix®)	co-administration may result in decreased clopidogrel active metabolite levels, platelet inhibition, and clopidogrel efficacy; clopidogrel requires metabolism through CYP2C19 to active metabolite and cimetidine is CYP2C19 inhibitor	cimetidine-clopidogrel combination should be avoided; H2RA alternatives (e.g., famotidine, ranitidine) that are not CYP2C19 inhibitors can be substituted for cimetidine	major (DrugReax) 2-major (CP)
cimetidine	dofetilide (Tikosyn®)	concurrent use may potentially increase dofetilide serum levels/ enhance pharmacologic effects (e.g., torsades de pointes) as dofetilide metabolized by CYP3A4, eliminated through renal and hepatic mechanisms; cimetidine inhibits dofetilide clearance through interference with active tubular secretion and moderate CYP3A4 inhibition	dofetilide manufacturer states that concurrent administration of dofetilide and cimetidine is contraindicated; medications without effect on dofetilide pharmacokinetics (e.g., omeprazole, ranitidine, antacids) are potential alternatives to cimetidine	contraindicated (DrugReax) 1-severe (CP)

Table 4: Major H2RA Drug-Drug Interactions (continued)				
Target Drug	**Interacting Drug**	**Interaction**	**Recommendations**	**Clinical Significance*+**
cimetidine	theophylline	adjunctive use may cause theophylline toxicity as cimetidine inhibits theophylline hepatic metabolism	adjunctive use possible if proper monitoring and/or dosage adjustments are made; order in which therapy initiated important - adding theophylline to existing cimetidine drug regimen can be safe as theophylline dosage titrated to acceptable serum concentrations, but adding cimetidine to existing theophylline regimen may enhance theophylline pharmacologic/ adverse effects; other available H2RAs do not significantly interact with theophylline and may be appropriate alternatives for cimetidine	major (DrugReax) 2-major (CP)
cimetidine	warfarin	combined use may result in increased INR and moderate to severe bleeding in some patients as cimetidine stereoselectively inhibits hepatic metabolism of warfarin R-isomer	adjunctive use possible if proper monitoring and/or dosage adjustments are made; order in which therapy is initiated is important - adding warfarin to existing cimetidine drug regimen can be safe as warfarin dosage titrated to acceptable monitoring parameter (e.g., INR), but adding cimetidine to existing warfarin regimen may enhance warfarin-induced hypoprothrombinemic response; other H2RAs do not significantly interact with warfarin - may be appropriate alternatives for cimetidine	moderate (DrugReax) 2-major (CP)
H2RAs	atazanavir (Reyataz®)	concurrent use may cause reduced atazanavir efficacy and increased resistance, as increased gastric pH with H2RAs causes decreased atazanavir solubility/ absorption/plasma levels	administer atazanavir either with and/or at least 10 hours after H2RA dose and monitor for decreased efficacy/increased resistance	major (DrugReax) 2-major (CP)

Table 4: Major H2RA Drug-Drug Interactions (continued)				
Target Drug	**Interacting Drug**	**Interaction**	**Recommendations**	**Clinical Significance*+**
H2RAs	select azole antifungals (itraconazole (Sporanox®), ketoconazole, posaconazole (Noxafil®)	combined use may result in reduced azole antifungal bioavailability, decreased maximum azole antifungal serum levels, and attenuated azole antifungal pharmacologic effects, as H2RAs increase gastric pH and azole antifungal oral absorption is dependent on acidic environment	posaconazole manufacturer recommends avoiding the posaconazole-cimetidine drug combination unless benefits outweigh risks; if H2RA-azole antifungal combination necessary, monitor patients carefully for reduced antifungal activity	major, moderate (DrugReax) 2-major (CP)
H2RAs	dasatinib (Sprycel®)	adjunctive administration for extended duration may result in reduced dasatinib exposure and serum levels as dasatinib dependent on acidic gastric pH for solubility and absorption	combined use not recommended; alternative acid suppressives (e.g., antacids) should be administered 2 hours before or 2 hours after dasatinib dose for optimal efficacy	major (DrugReax) 1-severe (CP)
H2RAs	delavirdine (Rescriptor®)	combined use for extended treatment duration may result in reduced delavirdine absorption, decreased delavirdine serum levels, and attenuated delavirdine efficacy as delavirdine is dependent on an acidic gastric pH for absorption; separating drug doses may not improve delavirdine absorption as H2RAs affect gastric pH for prolonged time	concomitant use not recommended; antacids may be alternative acid suppressive therapy, with antacid and delavirdine doses separated by at least one hour	major (DrugReax) 2-major (CP)

**CP = Clinical Pharmacology*

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